The isolation of iodides VIII-XIV and XVIII and XIX was accomplished as follows. The mixture was cooled and treated with ether, and the resulting precipitate or resinous mass was dissolved by heating in ethanol. An equal volume of 10% potassium iodide solution was added to the resulting solution and the mixture was cooled. The isolated dyes were purified by recrystallization from ethanol.

Dimethylidynemerocyanines (XV and XVI). These dyes were obtained by condensation of 0.001 mole of the ethiodide of XX or XXII with 0.001 mole of 3-ethyl-5-acetanilidomethylene-rhodanine in 4-6 ml of anhydrous ethanol in the course of 1 h while refluxing in the presence of 0.001 mole of triethylamine. The mixture was cooled, and the dye was removed by filtration and purified by recrystallization from ethanol.

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SYNTHESES IN THE BENZO-2, 1,3-THIADIAZOLE SERIES.

II.* DERIVATIVES OF 1,2,5-THIADIAZOLO]3,4-h]QUINOLINE AND BENZO-2, 1, 3-THIADIAZOLO]4, 5-h]-1,6-NAPHTHYRIDINE

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UDC 547.794.3'831'836.3.07

Derivatives of 1,2,5-thiadiazolo[3,4-h]quinoline and benzo- 2,1,3-thiadiazolo-[4, 5-h]-1, 6-naphthyridine were synthesized from 4-aminobenzo-2, 1, 3-thiadiazole.

We have accomplished the synthesis of 1,2,5-thiadiazole[3,4-h]quinoline derivatives [2, 3] (Table 1), their conversion to potential antiparasitic compounds (IIg and IIh), and the transition to a new heterocyclic system — benzo-2,1,3-thiadiazolo[4,5-h]-1,6-naphthyridine.

*See [1] for communication I.

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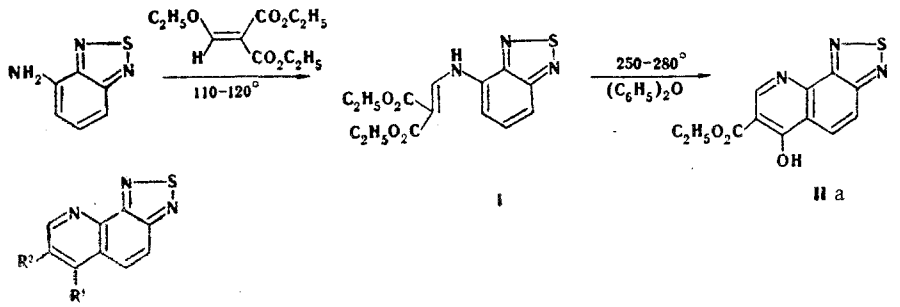
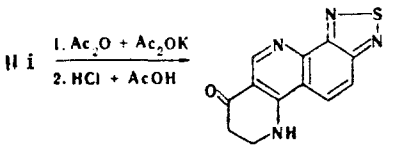


IIb, в R^1=OH; d, e, f R^1=Cl; g R^1=NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$; h, i R^1= =NH(CH$_2$)$_2$COOH; IIb, e, i R^2=COOH; c, f, g R^2=H; d R^2=COOC$_2$H$_5$

When thiadiazolo[3,4-h]quinoline hydroxy derivatives (IIa-c) are heated with phosphorus oxychloride or thionyl chloride, the hydroxyl group is readily substituted by halogen (IId-f); in the case of IIe the intermediate acid chloride was not isolated but was immediately converted to acid IIe.

The corresponding amino derivatives (IIg, h) are formed by the reaction of IId, f, with amines. The analog (IIg) of the antimalarial preparation chloroquine, which contains a thiadiazole group, did not show activity in tests on *P. berghei* (white mice).

Compound IIi was converted to the benzo-2,1,3-thiadiazolo[4,5-h]-1,6-naphthyridine derivative (IIIa) by cyclization in acetic anhydride in the presence of potassium acetate [4-6]:



The N-acetyl derivative formed in this reaction was hydrolyzed, without purification to IIIa. The presence of a keto group in IIIa was confirmed by its IR spectrum (ν_{CO} 1676 cm^{-}) and the formation of a hydrazone.

TABLE 1. 1,2,5-Thiadiazolo[3,4-h]quinoline Derivatives (IIa-i)

Compound	mp, °C	Empirical formula	Found, %		Calc. %		Yield, %
			N	S	N	S	
IIa	285—287	$C_{12}H_9N_3O_3S$	15,5	11,6	15,3	11,7	86
IIb	304—306[a]	$C_{10}H_5N_3O_3S$	16,8	12,8	17,0	13,0	85
IIc	277—280	$C_9H_5N_3OS$	20,3	15,6	20,7	15,8	89
IId	158—160	$C_{12}H_8ClN_3O_2S$[b]	14,6	10,9	14,3	10,9	84
IIe	309—310[a]	$C_{10}H_4ClN_3O_2S$[c]	15,7	12,1	15,8	12,1	81
IIf	213—215	$C_9H_4ClN_3S$[d]	19,3	—	19,0	—	82
IIg	146—148	$C_{18}H_{25}N_5S$	20,7	9,1	20,4	9,4	55
IIh	234—236[a]	$C_{15}H_{14}N_4O_4S$	15,9	9,1	16,2	9,2	87
IIi	251—253[a]	$C_{13}H_{10}N_4O_4S$	17,4	10,1	17,6	10,1	81

[a]With decomposition. [b]Found: Cl 12.1%. Calculated: Cl 12.1%. [c]Found: Cl 13.7%. Calculated: Cl 13.4%. [d]Found: Cl 16.3%. Calculated: Cl 16.0%. [e]This is the yield of the recrystallized compound.

EXPERIMENTAL

The melting points of the compounds were determined with a Mel-Temp apparatus [7] and were not corrected. The UV spectra of alcohol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

Diethyl N-[4-(Benzo-2,1,3-thiadiazolyl]aminomethylenemalonate (I). A mixture of 27.4 g (0.2 mole) of 4-aminobenzo-2,1,3-thiadiazole and 43.2 g (0.2 mole) of ethoxymethylenemalonic ester was heated at 110-120° for 1.5 h with removal of the liberated alcohol by distillation. The mixture was cooled, upon which it solidified. The red-brown product was triturated and washed with alcohol to give 55.3 g (86%) of yellow-orange needles with mp 122-123° (from alcohol). Found: N 13.4; S 9.9%. $C_{14}H_{15}N_3O_4S$. Calculated: N 13.1; S 10.0%.

Ethyl 6-Hydroxy-1,2,5-thiadiazolo[3,4-h]quinoline-7-carboxylate (IIa). A solution of 35.35 g (0.11 mole) of I in 175 ml of diphenyl ether was refluxed for 1 h, after which it was cooled and diluted with 100 ml of hexane. The resulting precipitate was removed by filtration and washed with hexane to give light-brown crystals [from dimethylformamide (DMF)].

6-Hydroxy-1,2,5-thiadiazolo[3,4-h]quinoline-7-carboxylate (IIb). A mixture of 27.5 g (0.1 mole of IIa, 14.0 g (0.35 mole) of sodium hydroxide, and 140 ml of water was refluxed until all of the solids had dissolved (∿ 1 h), and the resulting solution was diluted with 100 ml of water, treated with activated charcoal, and filtered. The filtrate was acidified with concentrated HCl, and the precipitate was removed by filtration, washed with water and alcohol, and crystallized from DMF to give light-brown crystals.

6-Hydroxy-1,2,5-thiadiazolo[3,4-h]quinoline (IIc). A 2.47-g (0.01 mole) sample of acid IIb was fused by heating to 300° on a metal bath and allowed to stand at this temperature for 10-15 min until the evolution of carbon dioxide bubbles ceased. The cooled solidified melt was pulverized and crystallized from DMF to give a yellow-green substance.

Ethyl 6-Chloro-1,2,5-thiadiazolo[3,4-h]quinoline-7-carboxylate (IId). A) A mixture of 5.5 g (0.02 mole) of IIa and 15 ml of phosphorus oxychloride was refluxed for 3 h, after which the excess phosphorus oxychloride was removed by vacuum distillation (water aspirator). Crushed ice and concentrated ammonium hydroxide were added until the mixture was alkaline, and the solid was removed by filtration, triturated in a mortar with ammonium hydroxide, removed by filtration, and washed with water. It was then air dried and extracted with hot ethyl acetate in a Soxhlet apparatus to give light-yellow-tinted crystals.

B) A mixture of 5.5 g (0.02 mole) of IIa, 16.6 g [10.0 ml (0.043 mole)] of thionyl chloride, and 10 ml of DMF was refluxed for 2 h. It was then cooled and treated with hexane, and the liberated solid was separated and treated with aqueous $NaHCO_3$ solution. The solid was removed by filtration and washed with water to give 4.5 g (86%) of a product with mp 158-160° (from alcohol). No melting-point depression was observed for a mixture of this product with a sample obtained by method A.

6-Chloro-1,2,5-thiadiazolo[3,4-h]quinoline (IIf). A mixture of 2.03 g (0.01 mole) of IIc and 10 ml of phosphorus oxychloride was refluxed for 1 h, after which the excess phosphorus oxychloride was removed by vacuum distillation. The residue was triturated with ammonium hydroxide, and the solid was separated and washed with water. Crystallization of the solid from alcohol–DMF gave colorless crystals.

6-Chloro-1,2,5-thiadiazolo[3,4-h]quinoline-7-carboxylic Acid (IIe). A mixture of 4.13 g (0.015 mole) of IIb, 20 ml of thionyl chloride, and 10 ml of DMF was refluxed for 1 h, after which it was vacuum evaporated. The residue was cooled and treated with 30 ml of water, and the mixture was refluxed for 2 h. It was then cooled, and the solid product was separated, washed with water, dried, and crystallized from DMF to give light-yellow crystals.

6-(5-Diethylamino-2-pentylamino)-1,2,5-thiadiazolo[3,4-h]quinoline (IIg). A mixture of 3.32 g (0.015 mole) of IIf and 9.6 g (0.06 mole) of 1-diethylamino-4-aminopentane was heated at 160° for 8 h, after which the volatile reaction products were removed by steam distillation. The residual dark-brown oil was dissolved in 10% hydrochloric acid, and the resulting solution was treated with activated charcoal and made alkaline with ammonia. The liberated oil was separated and dissolved in benzene, and the solution was treated with activated charcoal and vacuum evaporated to dryness. The residue was crystallized from

heptane to give light-yellow crystals.

Ethyl 6-(2-Carboxyethylamino)-1,2,5-thiadiazolo[3,4-h]quinoline-7-carboxylate (IIh). A mixture of 14.65 g (0.05 mole) of acid IId, 8.9 g (0.1 mole) of β-alanine, and 50 g of phenol was stirred at 120-125° for 3 h, after which the phenol was removed by steam distillation. The solid residue was separated, washed with water and alcohol, and air dried. The product was purified by reprecipitation from sodium carbonate solution by the addition of acetic acid to give a lemon-yellow crystalline product.

6-(2-Carboxyethylamino)-1,2,5-thiadiazolo[3,4-h]quinoline-7-carboxylic Acid (IIi). A mixture of 13.83 g (0.04 mole) of IIh, 6.72 g (0.12 mole) of potassium hydroxide, 200 ml of methanol, and 90 ml of water was refluxed for 1 h, and the resulting solution was filtered and acidified with hot acetic acid. The solution was cooled, and the precipitated solid was separated, washed with water, and crystallized from DMF to give a lemon-yellow crystalline product. UV spectrum, λ_{max}, nm (log ε): 228 (4.07), 251 (4.55) shoulder, 258 (4.75), 290 (4.43), and 405 (3.83).

6-Oxo-6,7,8,9-tetrahydrobenzo-2,1,3-thiadiazolo [4,5-h]-1,6-naphthyridine (IIIa). A mixture of 7.95 g (0.025 mole) of acid IIi, 6.9 g (0.05 mole) of freshly fused potassium acetate, and 100 ml of acetic anhydride was allowed to stand on a boiling-water bath for 2 h, after which the temperature of the reaction mixture was gradually raised to 115°, and the mixture was heated at this temperature for 10-20 min until carbon dioxide evolution ceased. The mixture was subjected to vacuum distillation, 100 ml of water was added to the residue, and the aqueous mixture was stirred and allowed to stand in a refrigerator for 12 h. The liberated material was separated, washed with water, and mixed with 15 ml of concentrated hydrochloric acid and 5 ml of acetic acid. The acidic mixture was heated and stirred at 100° for 30 min, after which it was evaporated to dryness, and the residue was made alkaline with 10% sodium hydroxide solution. The alkaline solution was stirred at room temperature for 1 h, and the solid material was separated and washed with water to give 4.17 g (64%) of shiny yellow-green crystals with mp > 360° (from DMF). UV spectrum, λ_{max}, nm (log ε): 212 (410), 247 (4.32) shoulder, 252 (4.34), 295 (4.34), 328 (3.66) shoulder, and 382 (3.61). Found: N 22.3; S 12.6%. $C_{12}H_8N_4OS$. Calculated: N 21.9; S 12.5%. The hydrazone (IIIb) of IIIa was prepared as follows. A mixture of 0.26 g (0.001 mole) of ketone IIIa, 2 ml of hydrazine hydrate, and 5 ml of DMF was refluxed for 1 h, after which it was cooled, and the liberated crystals were separated and washed with water to give 0.25 g (96%) of orange crystals that did not melt on heating up to 360°. An analytical sample was obtained by crystallization from DMF. Found: N 31.5; S 11.7%. $C_{12}H_{10}N_6S$. Calculated: N 31.1; S 11.9%.

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